REMARKS

Claims 23-26, 28, 30-37, 127-129 are pending. Claims 23-26, 28, 30-32 and 127 are currently presented for examination. Claims 1-22, 27, 29, 36 and 38-126 canceled and claims 33-35, 37 and 128 are withdrawn without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of any or all of the canceled and/or withdrawn claims in one or more continuing applications.

Claims 23-26, 30-32 and 127 are amended. Support for these amendments can be found in the claims as originally filed and throughout the specification. For example, support for the amendment to the claims can be found at paragraphs **[0007]** and **[0017]** of the specification, at original claim 29, and elsewhere throughout the specification as originally filed. Accordingly, no new matter is added by way of these amendments.

Claim 129 is new. Support for claim 129 can be found in the specification as originally filed. For example, support for claim 129 can be found at paragraph **[0388]** and elsewhere throughout the specification as originally filed. As such, new claim 129 does not constitute new matter.

Information Disclosure Statement

The Examiner did not consider references listed as 2-8 in the Information Disclosure Statement (IDS) submitted on June 17, 2005 because the citations allegedly lacked publication dates. Applicants submit a supplemental IDS herewith, which includes publication dates for references 2-8. Copies of each of these references are also submitted herewith.

Rejection of claim 31 under 35 U.S.C. § 112, second paragraph

The Examiner rejects claim 31 as being indefinite for failing to particularly point out with particularity the claimed subject matter. Specifically, the Examiner asserts that it is unclear how an antisense nucleic acid comprising a nucleotide sequence can be complementary to an amino acid sequence.

In order to move the claims rapidly to allowance, Applicants have amended claim 31 to recite an antisense nucleic acid complementary to at least a portion of a nucleic acid encoding

said NF-HEV polypeptide or a biologically active fragment thereof. In view of this amendment, Applicants request the examiner to withdrawn rejection of claim 31.

Rejection of claims 23-26, 28-32 and 127 under 35 U.S.C. § 112, first paragraph (written description)

The Examiner rejects claims 23-26, 28-32 and 127 as allegedly failing to comply with the written description requirement under 35 U.S.C. § 112, first paragraph. In particular, the Examiner asserts that the claimed subject matter was not described in the specification so as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed subject matter. More specifically, the Examiner asserts that the instant application fails to provide a structure of a single compound for use in the claimed methods, and thus, fails to adequately describe the above-rejected claims. Applicants respectfully disagree.

Applicants maintain that claims 23-26, 28-32 and 127 are adequately described by the specification. The Examiner is reminded that working examples are not necessary to meet the written description requirement. All that is required is that the Applicant provide a representative number of species to adequately describe the claimed genus. In the present case, the specification discloses nucleic acid sequences (SEQ ID NOs: 1-3) which encode polypeptides corresponding the NF-HEV polypeptides (SEQ ID NOs: 4-6) from three different organisms. The nucleic acid sequences complementary to SEQ ID NOs: 1-3 can be readily determined by those of ordinary skill in the art. Paragraphs **[0355]** to **[0381]** of the instant application describe numerous antisense nucleic acids and siRNA molecules of specific lengths and types that can be constructed from these complementary sequences. Furthermore, paragraphs **[0355]** to **[0381]** of the instant application describe extensive chemical modification that can be made to such molecules in order to optimize their performance *in vivo*. As such, at the time of filing the instant application, Applicants have described a sufficient number of different compounds that can reduce the level or activity of NF-HEV to comply with the written description requirement.

In view of the foregoing remarks, Applicants respectively submit that claims 23-26, 28, 30-32 and 127 are in compliance with the written description requirement and request that the

Examiner withdraw the rejection of these claims under 35 U.S.C. 112, first paragraph. In light of the cancellation of claim 29, the above written description rejection with respect to this claim is moot.

Rejection of claims 23-26, 28-30, 32 and 127 under 35 U.S.C. § 112, first paragraph (enablement)

Claims 23-26, 28-30, 32, and 127 are rejected under U.S.C. 112, first paragraph as allegedly lacking enablement. First, the Examiner alleges that the application does not enable the skilled artisan to ameliorate symptoms of a condition associated with inflammation by increasing the level or activity of NF-HEV. Second, the Examiner asserts that the specification does not enable the claimed therapeutic effects because it would require undue experimentation for a skilled artisan to administer molecules, other than antisense nucleic acids, so as to achieve the expected therapeutic effects.

Applicants maintain that, based on the teachings of the instant specification, a skilled artisan could practice the subject matter of the above-rejected claims without undue experimentation. However, in order to rapidly move the instant application to issuance, Applicants have amended independent claim 23 to replace the term "modulating" with "reducing." As acknowledged by the Examiner at page 7 of the Office Action, the specification is enabling for a method of ameliorating symptoms of an inflammatory condition by inhibiting NF-HEV activity. Accordingly, Applicants request that the first aspect of the enablement rejection be withdrawn.

Applicants also maintain that the specification provides ample guidance for those of ordinary skill in the art to administer inhibitors of NF-HEV to reduce the level or activity of NF-HEV and thereby ameliorate symptoms of a condition associated with inflammation. At page 10 of the Office Action, the Examiner asserts that the claims are enabled only for "a method of ameliorating symptoms of an inflammatory condition in a subject by reducing the level of NF-HEV comprising administering a single-stranded antisense nucleic acid targeted to a fragment of the NF-HEV mRNA." Although applicants agree that the claims are enabled with respect to the administration of antisense nucleic acids, they do not agree that the specification is so limiting.

For example, Applicants provide guidance for making and administering siRNAs capable for reducing the level or activity of NF-HEV (see Examples 20 and 21). Furthermore, the declaration of Dr. Jean-Philippe Girard that is provided herewith, shows that a skilled artisan can practice the examples disclosed in the application without any undue experimentation so as to readily obtain siRNA molecules that inhibit the level or activity of NF-HEV, thereby resulting in a decrease in pro-inflammatory cytokine levels. In particular, the Declaration of Dr. Girard shows that siRNAs specific to NF-HEV reduce the level of NF-HEV mRNA, which in turn, causes a reduction in the level of pro-inflammatory chemokine, CCL2/MCP-1, when tested in cultured human primary endothelial cells (HUVECs). As such, it is clear that the guidance provided by the specification is sufficient for those of ordinary skill in the art to practice the subject matter of the above-rejected claims without undue experimentation.

In view of the foregoing remarks and amendments, Applicants respectfully request that the Examiner withdraw the rejection of claims 23-26, 28-30, 32 and 127 under 35 U.S.C. § 112, first paragraph. In light of the cancellation of claim 29, the above enablement rejection with respect to this claim is moot.

Rejection of claims 23-25, 28-31 and 127 under 35 U.S.C. § 102

The Examiner rejects claims 23-25 and 28-31 under 35 U.S.C. §102(b) as allegedly being anticipated by Ruben et al. (WO 99/38881). Also, the Examiner rejects claims 23-25 and 28-31 under 35 U.S.C. §102(e) as allegedly being anticipated by Jiang et al. (US 2003/0087818). Finally, the Examiner rejects claims 23-25, 28-31 and 127 under 35 U.S.C. §102(e) as allegedly being anticipated by Woolf et al. (US 2007/0015145).

Applicants maintain that each of claims 23-25, 28-31 and 127 are novel in over the above-cited references. It is well established that a claim is anticipated only if each and every element as set forth in the claim is found in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Independent claim 23 recites "a method of ameliorating symptoms of a condition associated with inflammation, wherein said method comprises identifying a subject having symptoms of a condition associated with chronic inflammation and reducing in said subject the level or activity

of the NF-HEV polypeptide or a biologically active fragment thereof, thereby ameliorating symptoms of a condition associated with inflammation. As set forth in detail below, none of the above-cited references disclose each and every element of this claim.

Applicants submit that Ruben et al. and do not disclose each and every element of the subject matter of independent claim 23. Ruben et al. disclose a nucleic acid sequence (SEQ ID NO: 35) having about 99.5% nucleotide identity with a portion of the nucleic acid encoding NF-HEV (SEQ ID NO: 1) of the instant application. Ruben et al. suggest that polynucleotides and polypeptides associated with SEQ ID NO: 35 can be used to treat generic disorders of the gastrointestinal tract or the vascular system. Ruben et al. do not disclose that SEQ ID NO: 35 is implicated in inflammatory conditions, let alone, chronic inflammatory conditions. Furthermore, Ruben et al. do not disclose the step of identifying a subject having symptoms of a condition associated with chronic inflammation, and then, reducing in said subject the level or activity of the NF-HEV polypeptide or a biologically active fragment thereof, thereby ameliorating symptoms of a condition associated with inflammation. Accordingly, Ruben et al. do not anticipate each and every element of claim 23.

Applicants submit that Jiang et al. do not disclose each and every element of the subject matter of independent claim 23. While Jiang et al. do disclose a nucleic acid of SEQ ID NO: 437, a portion of which shows some sequence similarity to a small portion of the nucleic acid encoding NF-HEV (SEQ ID NO: 1) of instant application, they suggest that SEQ ID NO: 437 is involved in cancer. Jiang et al. do not disclose that SEQ ID NO: 437 is relevant to inflammatory conditions, let alone chronic inflammatory conditions. Furthermore, Jiang et al. do not disclose the step of identifying a subject having symptoms of a condition associated with chronic inflammation, and then, reducing in said subject the level or activity of the NF-HEV polypeptide or a biologically active fragment thereof thereby ameliorating symptoms of a condition associated with inflammation. Accordingly, Jiang et al. do not anticipate each and every element of claim 23.

Applicants submit that Woolf et al. do not disclose each and every element of the subject matter of independent claim 23. Woolf et al. disclose a nucleic acid (SEQ ID NO: 11450), which the Examiner alleges to be identical to the nucleic acid encoding NF-HEV (SEQ ID NO:1) of the

present application. Woolf et al. also allegedly disclose that this nucleic acid may be associated with pain. Woolf et al., however, fail to disclose a step of identifying a subject having symptoms of a condition associated with chronic inflammation, and then, reducing in said subject the level or activity of the NF-HEV polypeptide or a biologically active fragment thereof thereby ameliorating symptoms of a condition associated with inflammation. Accordingly, Woolf et al. do not disclose each and every element of claim 23.

In their remarks above, Applicants have discussed the novelty of independent claim 23. Each of the other above-rejected claims (claims 24-25, 28, 30-31, and 127) depend from claim 23. Because dependent claim 23 is novel, claims 24-25, 28, 30-31, and 127 are also novel. Accordingly, Applicants request the withdrawal of the rejections of claims 23-25, 28, 30, 31 and 127 under 35 U.S.C. § 102. In view of the cancellation of claim 29, the above anticipation rejection with respect to this claim is rendered moot.

Rejection of claims 23-25, 28-31, and 127 under 35 U.S.C. § 103

The Examiner rejects claims 23-25, 28-31, and 127 under U.S.C. 103(a) as allegedly being obvious over Kasuya et al (*Acta Neurochirurgica Supplement,* 2001, 77:13-16) in view of Orr et al. (*Current Opinion in Molecular Therapeutics*, 2000, 2:325-331). In particular, the Examiner asserts that Kasuya et al. disclose a gene, DVS27, which encodes an mRNA and protein identical to SEQ ID NOs: 1 and 4, respectively. The Examiner also asserts that Kasuya et al. disclose that DVS27 expression is upregulated in response to inflammatory stimuli. Although the Examiner acknowledges that Kasuya et al. do not disclose antisense as a means for reducing the level or activity of the DSV27 polypeptide, the Examiner alleges that Orr et al. disclose general antisense-mediated therapeutics that can be used for cytokine reduction. The Examiner then alleges that a skilled artisan would be motivated to combine the disclosure of Kasuya et al. with that of Orr et al. in order to arrive at the subject matter of the above-rejected claims with a reasonable expectation of success.

Regarding rejections of claims as being obvious, the Examiner has the burden under 35 U.S.C. § 103(a) to establish a *prima facie* case of obviousness. *In re Piasecki*, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-87 (Fed. Cir. 1984). To establish a *prima facie* case of obviousness,

however, prior art must teach or suggest all the claim limitations. "Examination Guidelines for Determining Obviousness Under 35 U.S.C. §103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*" Federal Register Vol. 72 No. 195 at 57528 (October 10, 2007). Furthermore, the Examiner must explain why the differences between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art. *Id.*

Applicants respectively submit that the combination of Kasuya et al. and Orr et al. does not teach or suggest all the limitations of independent claim 23. Kasuya et al. disclose only that DVS27 might be involved in inflammatory events (see column 2 at page 16 of Kasuya et al.). Kasuya et al. do not teach or suggest that DVS27 is associated with chronic inflammation nor do they teach or suggest the step of identifying a subject having symptoms of a condition associated with chronic inflammation, and then, reducing in said subject the level or activity of the NF-HEV polypeptide or a biologically active fragment thereof thereby ameliorating symptoms of a condition associated with inflammation. Orr et al. disclose that patent applications have been filed that claim antisense nucleic acids to genes encoding the cytokines, lymphocyte function-associated antigen (LFA3), TNFα and cyclooxygenase. Orr et al. do not teach or suggest that DVS27 is involved in chronic inflammation or that a subject suffering from chronic inflammation should be identified for treatment with an antisense molecule targeted to NF-HEV. Furthermore, a skilled artisan would not have been motivated to apply the teaching of Orr et al. to those of Kasuya et al. since NF-HEV is not a cytokine but rather a transcription factor.

Even if we assume, *arguendo*, that a skilled artisan would have been motivated to further test DVS27 using antisense nucleic acids as alleged by the Examiner, the combination of Kasuya et al. and Orr et al. would still not teach all of the elements of independent claim 23. At best, such experiments might confirm that DVS27 is upregulated in response to inflammatory events as suggested by Kasuya et al. However, disclosure of this protein's involvement in chronic inflammation, and disclosure of a step of identifying a subject having symptoms of a condition associated with chronic inflammation would still be lacking. Accordingly, the combination of Kasuya et al. and Orr et al. does not teach or suggest all of the elements of independent claim 23 or any of the above-rejected claims that are dependent thereon.

In view of the foregoing remarks and amendments, Applicants request that the Examiner withdraw the rejection of claims 23-25, 28, 30, 31 and 127 under 35 U.S.C. § 103. In light of the cancellation of claim 29, the above obviousness rejection with respect to this claim is rendered moot.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

Applicants believe that all outstanding issues in this case have been resolved and that the present claims are in condition for allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is invited to contact the undersigned at the telephone number provided below in order to expedite the resolution of such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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